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Patentanmeldung Nr. Patent application No. Demande de brevet n°

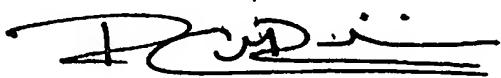
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For the President of the European Patent Office

Le Président de l'Office européen des brevets
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R C van Dijk

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SUISSE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

New chiral diols, their manufacture and ligands and catalysts derived therefrom

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AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LU MC NL PT SE SK TR

New chiral diols, their manufacture and ligands and catalysts derived therefrom

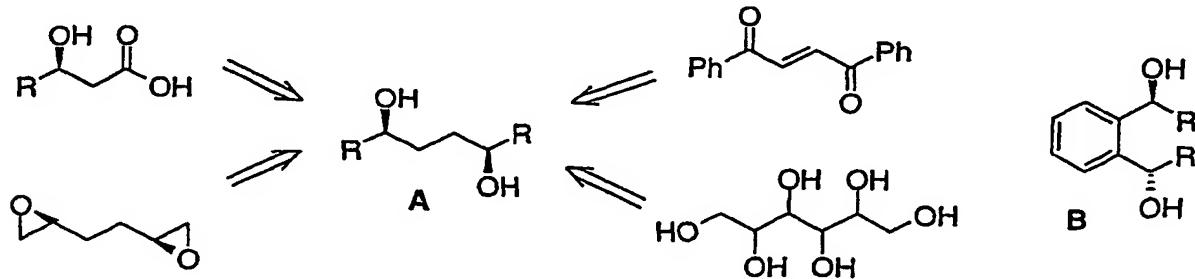
FIELD OF THE INVENTION

The present invention relates to a method for the preparation of C_2 -symmetric 1,4-diols that makes use of the metallation of pure enantiomers of α -(aryl or heteroaryl)- α -substituted alkanol compounds or the use of said alkanol compounds in the preparation of C_2 -symmetric 1,4-diols; novel C_2 -symmetric 1,4-diols in enantiomerically pure form; and methods of use or their use in the synthesis of chiral ligands which find use to produce catalysts for a variety of asymmetric transformations such as hydrogenations, allylations or alkylations.

BACKGROUND OF THE INVENTION

Chiral enantiomerically pure 1,4-diols of type A (see Scheme I below; R = organic moieties) have been utilized in the synthesis of ligands, with the DuPHOS- and BPE-ligands constituting a particular well known example (Burk, M. J. *J. Amer. Chem. Soc.* 1991, 113, 8518). Despite of their relatively simple structure, there are only few methods known for their synthesis. One approach utilises the Kolbe-coupling of enantiomerically pure 3-hydroxy alkanoates (Burk, M. J., Feaster, J. E.; Harlow, R. L.; *Tetrahedron: Asymmetry* 1991, 2, 569). Another approach utilizes the enantioselective reduction of 1,4-diketones (Quallich, G. J., Keavey, K. N., Woodall, T. M. *Tetrahedron Lett.* 1995, 36, 4729), the double alkylation of enantiopure 1,2-5,6-diepoxy hexane (Machinaga, N., Kibayashi, C. *Tetrahedron Lett.* 1990, 31, 3637), or the multistep functionalisation of carbohydrate derivatives (see for example: Stürmer R., Börner A., Holz J., Voss G. US 6,043,396).

Scheme I:

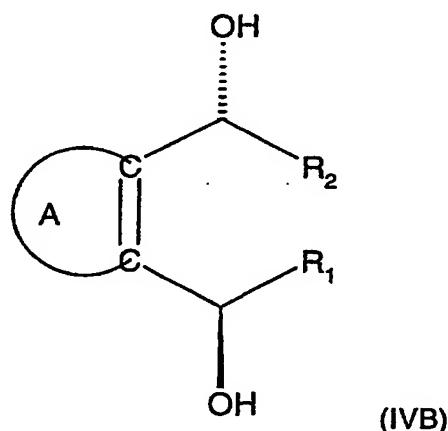
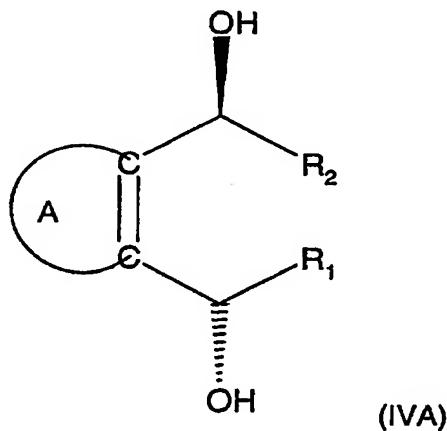


(Doucet H., Ohkuma T., Murata K., Yokozawa T., Kozawa M., Katayama E., England A. F., Ikariya T., Noyori R. *Angew. Chem., Int. Ed. Engl.* 1998, 37, 1703).

The new principle is to start from the enantio-pure compounds of the formula IA and IB, where surprisingly it has been found that the enantiopurity of the chiral atom present is conserved and at the same time it is possible to obtain the newly introduced chiral atom in pure chiral form under the direction of the chiral atom already present.

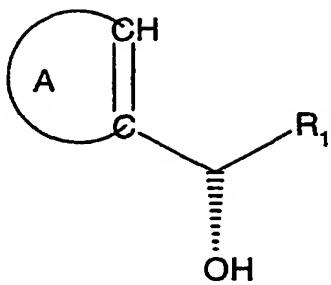
Specific Description of the invention

The invention relates in a first preferred embodiment to a process or method for the preparation of an enantiomerically pure C_2 -symmetric 1,4-diols of the formula IVA or IVB,

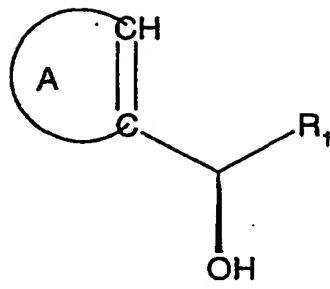


wherein ring A which includes the shown double bond forms a mono-, di- or polycyclic aromatic or heteroaromatic ring and R_1 and R_2 are, independently of each other, an organic moiety,

the process or method comprising reacting an α -(aryl or heteroaryl)- α -substituted alkanol compound of the formula IA (for the synthesis of a compound of the formula IVA) or IB (for the synthesis of a compound of the formula IVB)

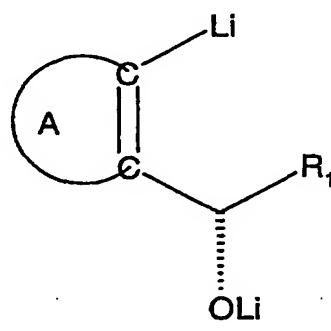


(IA)

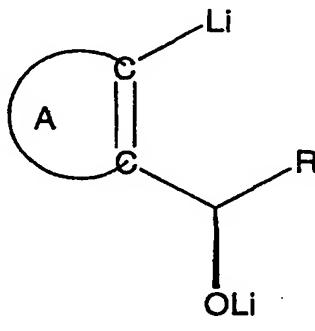


(IB)

wherein ring A and R₁ are as defined under formula IVA and IVB, with a lithiating reagent, optionally in the presence of a tertiary nitrogen base, obtaining an intermediate of the formula IIA (from IA) or IIB (from IB),



(IIA)

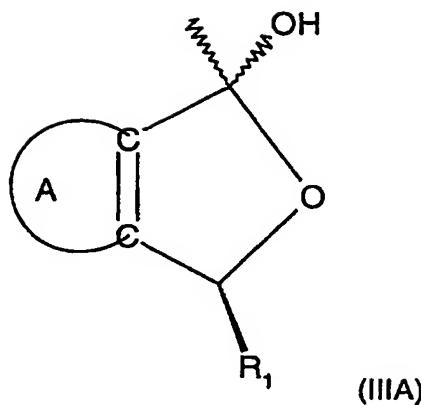


(IIB)

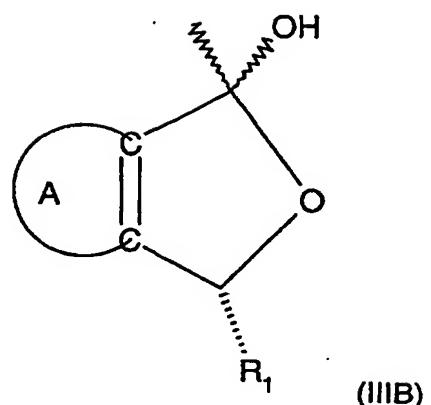
wherein ring A and R₁ have the meanings given under compounds of the formulae IVA and IVB.

These lithiated compounds then allow for two ways of producing the compounds of the formulae IVA or IVB.

In a first preferred variant, the lithiated product of the formula IIA or IIB, respectively, is then reacted with an N,N-di-alkyl-formamide to a hemiacetal compound of the formula IIIA (from IIA) or IIIB (from IIB),



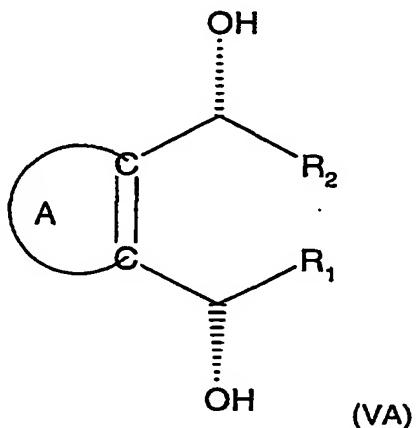
(IIIA)



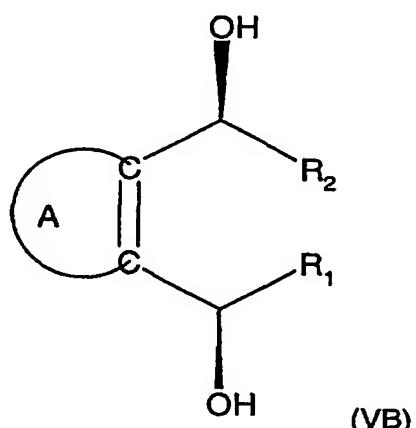
(IIIB)

wherein ring A, R₁ and R₂ have the meanings indicated for compounds of the formula IVA and IVB, and subsequently reacted with a Grignard reagent of the formula R₂MgX wherein R₂ is an organic moiety and X is halogen (or, alternatively, using corresponding lithium, zinc or other metal comprising compounds that allow for introduction of R₂, which may lead to increased selectivity and thus constitutes a preferred alternative) to yield the corresponding compounds of formula IVA (from IIIA) and IVB (from IIIB) given above.

Surprisingly, the higher the temperature used for the Grignard reaction, the higher selectivity towards the C₂-symmetric diols over the compounds of the formula VA (from IIIA) and VB (from IIIB),



(VA)



(VB)

wherein ring A, R₁ and R₂ have the meanings indicated for compounds of the formula IVA and IVB, is formed.

The reaction with the N,N-dialkylformamide takes place in the reaction mixture resulting from the lithiation.

In a second preferred variant, instead of the reaction with the the N,N-dialkylformamide an aldehyde of the formula VI



wherein R_2 is as defined for compounds of the formulae IVA and IVB, is reacted with the intermediate of the formula IIA to yield a compound of the formula IVA (and the meso by-product of the formula VA) or of the formula IIB to yield a compound of the formula IVB (and the meso by-product of the formula VB).

This reaction is very convenient in that it represents a one-pot reaction, still allowing for the use of the easily available starting materials of the formula IA or IB, respectively.

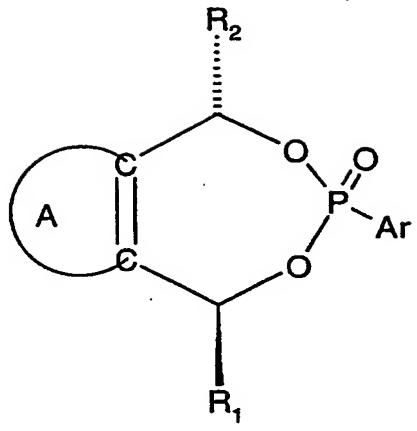
The invention also relates to the novel compounds of the formula IVA and IVB wherein ring A, R_1 and R_2 are as defined for a compound of the formula IVA or IVB with the proviso that R_1 and R_2 are not simultaneously methyl or ethyl, preferably not simultaneously alkyl, more preferably not identical.

The invention also relates to the use of compounds of the formula IVA or IVB or methods using these compounds in the synthesis of ligands.

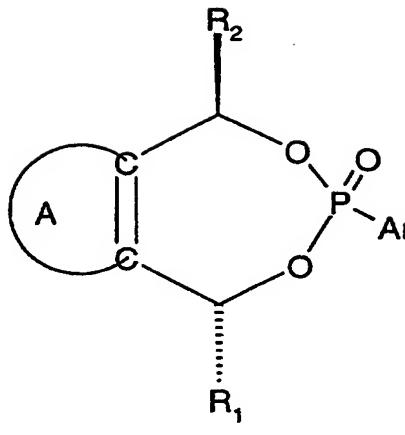
One preferred use/method using these compounds of formula IVA or IVB in the manufacture of ligands is where a compound of the formula IVA or VIB, or either a mixture of a compound of the formula IVA and of the formula VA given below; or a mixture of a compound of the formula IVB and of the formula VB given below; or a compound of the formula VA given below or of the formula VB given below; respectively, is reacted with an aryl phosphinic acid halogenide of the formula VII;



wherein Ar is aryl, especially phenyl, and Hal is halogen, especially chloro, in the presence of a base resulting in the formation of a phosphonate ester compound of the formula VIIA (from IVA) or VIIIB (from IVB), respectively,



(VIIIA)



(VIIIB)

wherein ring A, R₁ and R₂ have the meanings indicated for compounds of the formula IVA and IVB and Ar is aryl, and then reacting a compound of the formula VIIIA or VIIIB with a phosphine of the formula IX or IX*,

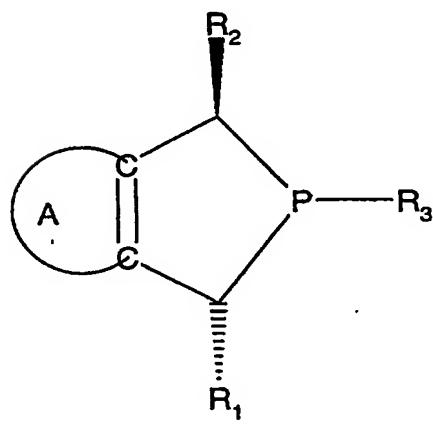


(IX)

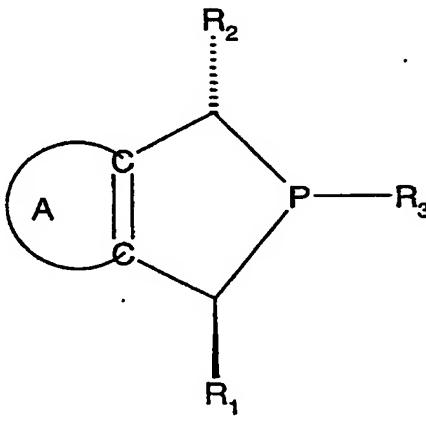


(IX*)

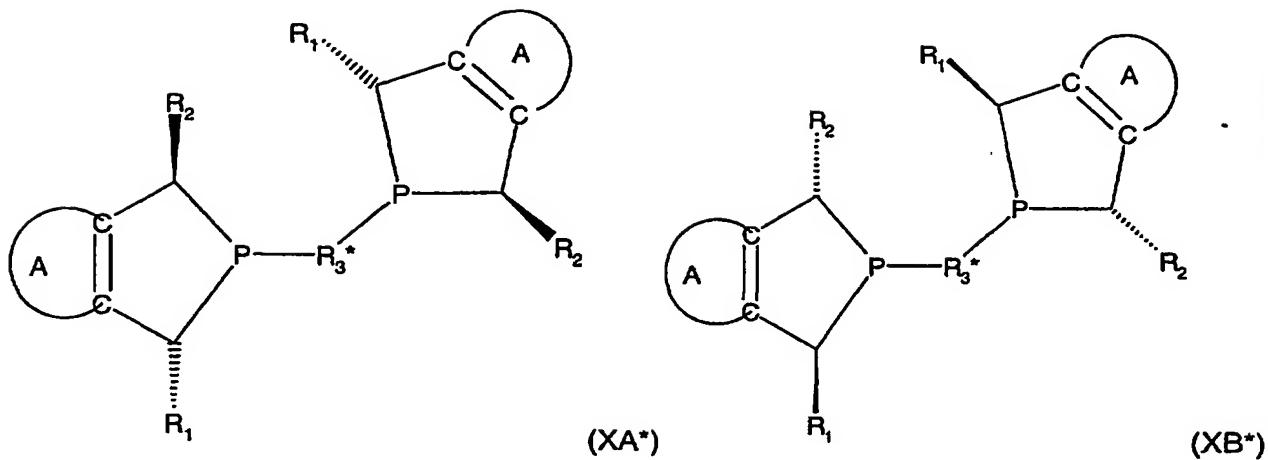
(or the corresponding borane adduct of any of these) wherein R₃ is a monovalent, R₃^{*} a bivalent organic moiety that can be bound to phosphorus, resulting in a phospholane compound of the formula XA or XA* (from VIIIA); or XB or XB* (from VIIIB), respectively,



(XA)



(XB)

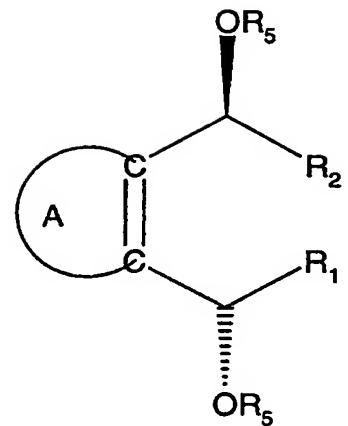


wherein ring A, R₁ and R₂ have the meanings indicated for compounds of the formula IVA or IVB and R₃ or R₃* is as defined under formulae IX and IX*, respectively.

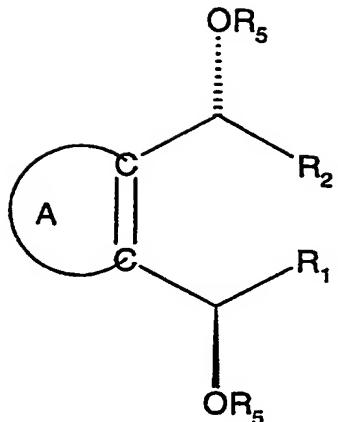
These are novel ligands. Therefore, the compounds of the formula XA, XA*, XB and XB* also are an embodiment of the invention, as well as their complexes with transition metals. These complexes can find use as catalysts for the asymmetric hydrogenation of C=N, C=C or C=O double bonds.

It is worthy to note, that there is little precedence for nucleophilic substitution with inversion of benzylic positions, as found in the reaction leading to compounds of the formula XA or XB, respectively.

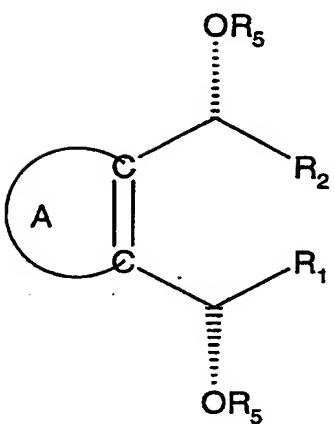
Alternatively, it is possible to react compounds of the formula IVA or IVB, preferably obtained and with the substituents as described herein, especially the corresponding preferred compounds, or mixtures of a compound of the formula IVA and VA or of the formula IVB and VB with an agent introducing an acyl protecting group, especially a lower alkanoyl or aroyl group, e.g. a pivaloyl or benzoyl group, such as with an acyl halogenide, e.g. an alkanoyl- or aroyl-halogenide, such as pivaloylchloride or benzoylchloride, preferably in the presence of a tertiary nitrogen base, to obtain the corresponding bis-hydroxy-protected compounds of the formulae IVA* (from IVA), IVB* (from IVB), or mixtures of a compound of the formula IVA* and VA* (from a mixture of a compound of the formula IVA and VA) or of a compound of the formula IVB* and VB* (from a mixture of a compound of the formula IVB and VB).



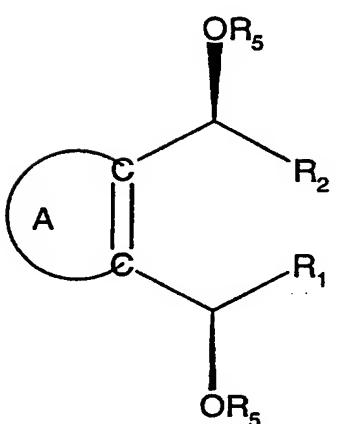
(IVA*)



(IVB*)



(VA*)



(VB*)

wherein ring A, R₁ and R₂ have the meanings indicated for compounds of the formula IVA and IVB and R₅ is acyl, especially alkanoyl or aroyl, such as pivaloyl or benzoyl.

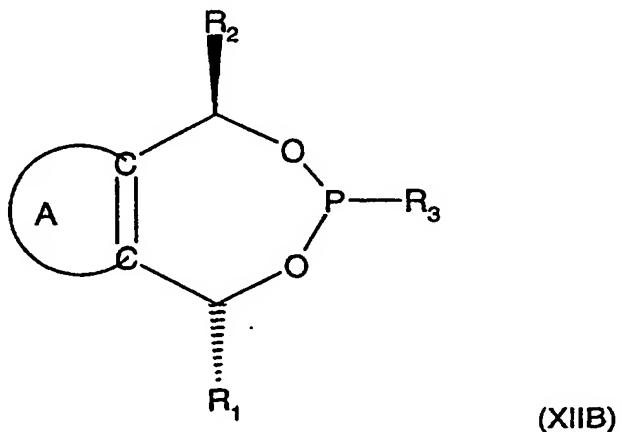
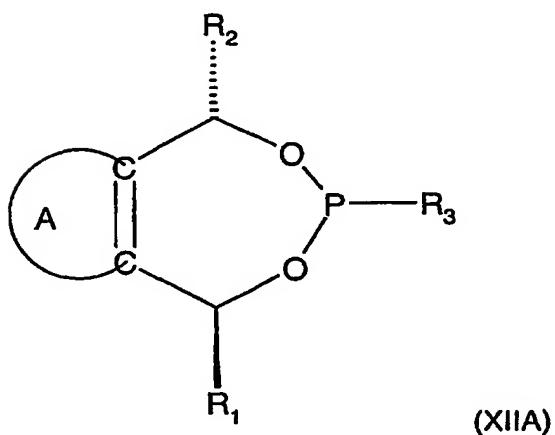
These compounds, especially those of the formula IVA* or IVB*, can then be reacted to the corresponding compounds of the formulae XA shown above with a compound of the formula IX shown above or a borane adduct thereof, or to a compound of the formula XA* shown above with a compound of the formula IX* shown above or a borane adduct thereof (from IVA*); or of the formula XB shown above with a compound of the formula IX shown above or a borane adduct thereof, or to a compound of the formula XB* shown above with a compound of the formula IX* shown above or a borane adduct thereof (from IVB*); in the case of mixtures of compounds of the formula IVA* and VA* or IVB* and VB* preferably after isolating the compounds of formula IVA* or IVB*, respectively, from the undesired enantiomer of the formula VA* or VB*, respectively, e.g. by chromatography or especially crystallization.

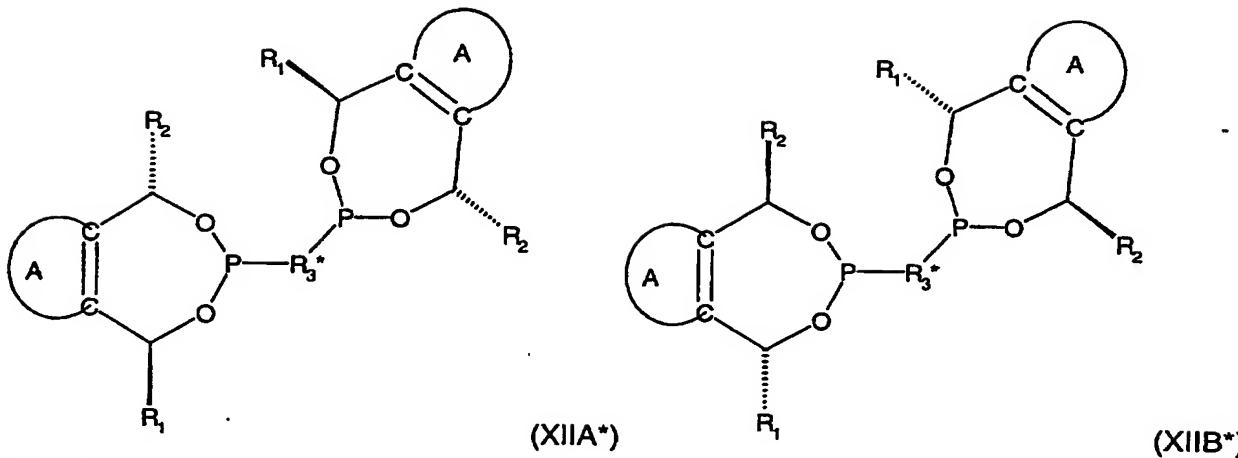
This route offers the advantage that the corresponding acyl derivatives, especially the pivaloyl or benzoyl derivatives, are more easy to crystallize so that the isolation of pure IVA* or pure IVB* is possible in a more convenient way than by chromatography or other separation methods.

Another preferred use/method using the compounds of formula IVA or IVB in the manufacture of ligands is where a compound of the formula IVA or VIB, respectively, is reacted with a compound of the formula XI or XI*,



wherein R_3 is a monovalent, R_3^* a bivalent organic moiety that can be bound to phosphorus and L is a leaving group, leading to ligands of the formula XIIA or XIIA* (from IVA) and/or XIIIB or XIIIB* (from IVB),

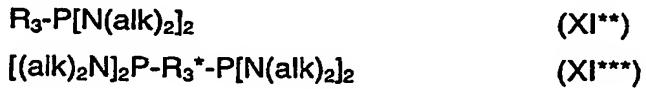




wherein ring A, R₁ and R₂ have the meanings indicated for compounds of the formula IVA and IVB and R₃ is a monovalent, R₃* a bivalent organic moiety that can be bound to phosphorus.

Also these compounds are novel ligands. Therefore, the compounds of the formula XIIA, XIIA*, XIIIB and XIIIB* also are an embodiment of the invention, as well as their complexes with transition metals. These complexes are especially of use the in 1,4-addition of Grignard compounds in the presence of Cu(I) to α,β -unsaturated carbonyl compounds or (e.g. with Rh, Ru, Ir as transition metals) for hydrogenation reactions, each of these reactions being possible especially in a highly stereoselective way.

As alternative within this second reaction way is where a compound of the formula IVA or VIB, respectively, is reacted with a compound of the formula XI** or XI***,



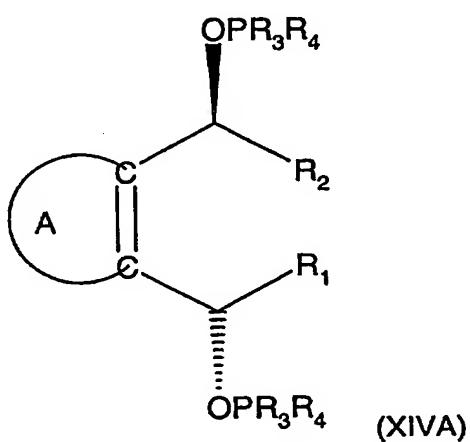
wherein R₃ is a monovalent, R₃* a bivalent organic moiety and alk is alkyl, especially lower alkyl, in particular methyl, under removal of the secondary amine HN(alk₂)₂, yielding the compound of formula XIIA or XIIA* (from IVA); or XIIIB or XIIIB* (from IVB) described above, respectively.

An third preferred use/method using the compounds of formula IVA or IVB in the manufacture of ligands is where a compound of the formula IVA or VIB, respectively, is reacted with a compound of the formula XIII,

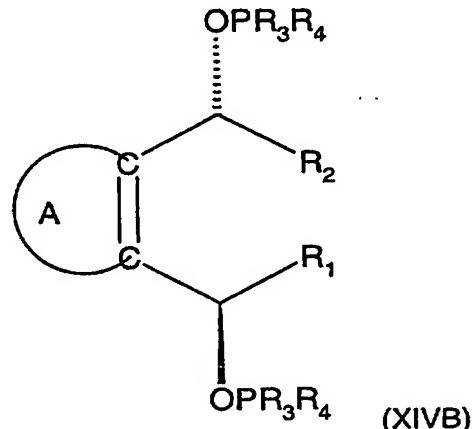


(XIII)

wherein R_3 and R_4 are organic moieties that can be bound to phosphorus and L is a leaving group, resulting in a compound of the formula XIVA (from IVA) or XIVB (from IVB), respectively,



(XIVA)



(XIVB)

wherein ring A, R_1 and R_2 are as defined for compounds of the formula XIVA or XIVB and R_3 and R_4 each are, independently of the other, an organic moiety that can be bound (stably) to phosphorus.

Also these compounds are novel ligands. Therefore, the compounds of the formula XIVA and XIVB also are an embodiment of the invention, as well as their complexes with transition metals. These complexes are especially of use in hydro-formylation or hydro-cyanation reactions (e.g. with Ni, Rh, Ru, Ir as transition metal), each of these reactions being possible especially in a highly stereoselective way.

As alternative within this third reaction way is where a compound of the formula IVA or VIB, respectively, is reacted with a compound of the formula XIII*,



(XIII*)

wherein R_3 is an organic moiety and alk is alkyl, especially lower alkyl, in particular methyl, under removal of the amine $HN(alk)_2$, yielding the compound if formula XIVA (from IVA) and/or XIVB (from IVB), respectively.

The formation of transition metal complexes of the compounds of the formula XA, XB, XIIA, XIIIB, XIVIA and/or XIVIB can follow methods that are known in the art. They are, for example, obtained by an exchange reaction between the chiral ligands and a complex of the chosen transition metal, in which the bond between metal and ligand must be more labile than the bond that will form between transition metal and phosphorus comprising ligand. Thus, the chiral ligand will replace the original ligand in the coordination to the metal, forming preferred coordination bonds.

The invention relates also to any novel single reaction step that is part of the synthesis of compounds of the formula IVA and/or IVB, as well as of those of formula XA and/or XB, as well as of those of the formula XIIA and/or XIIIB, as well as those of the formula XIVIA and/or XIVIB, or complexes of the ligands of the formulae XA, XB, XIIA, XIIIB, XIVIA and/or XIVIB, as well as to any novel intermediate formed during these synthesis steps.

If not indicated otherwise, the symbols and general expressions used above and below preferably have the following meanings:

A mono-, di- or polycyclic aromatic ring A is preferably unsubstituted or substituted arylene (with the two bonds to the rest of the molecule, that is, extending from the double bond forming part of ring A, bound at vicinal C-atoms) wherein aryl is as defined below.

In "unsubstituted or substituted", "substituted", wherever used for a moiety, means that one or more hydrogen atoms in the respective molecule, especially up to 5, more especially up to three, of the hydrogen atoms are replaced by the corresponding number of substituents which preferably are independently selected from the group consisting of alkyl, especially lower alkyl, for example methyl, ethyl or propyl, fluoro, fluoro-lower alkyl, for example trifluoromethyl, C₆-C₁₆-aryl, especially phenyl or naphthyl (where C₆-C₁₆-aryl, especially phenyl or naphthyl, is unsubstituted or substituted by one or more, especially up to three moieties selected from lower alkoxy, N,N-di-lower alkylamino, N-phenyl-lower alkylamino, N,N-bis(phenyl-lower alkyl)-amino, and fluoro-lower alkyl, e.g. trifluoromethyl), C₃-C₁₀-cycloalkyl, lower alkoxy, for example methoxy, phenyl-lower alkoxy, N,N-di-lower alkylamino, N-phenyl-lower alkylamino, N,N-bis(phenyl-lower alkyl)-amino and di-lower alkylamino. It goes without saying that substituents are only at positions where they are chemically pos-

sible, the person skilled in the art being able to decide (either experimentally or theoretically) without inappropriate effort which substitutions are possible and which are not.

Aryl (also in arylene) preferably has a ring system of not more than 24 carbon atoms, especially not more than 16 carbon atoms, is preferably mono-, bi- or tri-cyclic, and is unsubstituted or substituted preferably as defined above under "Substituted"; for example, aryl is selected from phenyl, naphthyl, indenyl, azulenyl and anthryl, and is preferably in each case unsubstituted or substituted phenyl or (especially 1- or 2-) naphthyl. Unsubstituted aryl is preferred. Unsubstituted aryl, preferably phenyl, is especially preferred as organic moiety. Aryl as ring A is also ferrocenyl which is one preferred aromatic moiety as ring A in any of the formulae carrying such a ring throughout this application and where the phenyl rings that form part of the ferrocenyl moiety are, in addition to the two bonds extending from the double bond in ring A in formulae IVA, IVB, IVA*, IVB*, IA, IB, IIA, IIB, IIIA, IIIB, VA, VB, VA*, VB*, VIIIA, VIIIB, XA, XB, XA*, XB*, XIIA, XIIIB, XIIA*, XIIIB*, XIVA and/or XIVB, unsubstituted or substituted, preferably by substituents as described above under "substituted", where preferably the phenyl ring from which the two bonds from ring A extend carries four hydrogen atoms, while the other ring that forms part of the ferrocenyl moiety is identical (including the substituents on the two bonds extending from the double bond shown in the mentioned formulae) or is phenyl that is unsubstituted or substituted by lower alkyl, such as methyl, ethyl and/or isopropyl.

A mono-, di- or polycyclic heteroaromatic ring A is preferably unsubstituted or substituted heteroarylene with heteroaryl as defined below (with the two bonds to the rest of the molecule, that is, extending from the double bond forming part of ring A, bound at vicinal C-atoms).

Heteroaryl is preferably a heterocyclic moiety that is unsaturated in the bonding ring and is preferably a monocyclic or in a broader aspect of the invention bicyclic or tricyclic ring; has 3 to 24, more preferably 4 to 16 ring atoms; wherein at least in the ring bonding to the radical of the molecule of formula I one or more, preferably one to four, especially one or two carbon ring atoms are replaced by a heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, the bonding ring preferably having 4 to 12, especially 5 to 7 ring atoms; heteroaryl being unsubstituted or substituted by one or more, especially 1 to 3, substituents independently selected from the group consisting of the substituents defined above

under "Substituted"; especially being a heteroaryl radical selected from the group consisting of imidazolyl, thienyl, furyl, pyranyl, thiopyranyl, benzofuranyl, benzimidazolyl, pyrazolyl, thi-azolyl, oxazolyl, pyridyl, pyrazinyl, pyrimidinyl, isoindolyl, indolyl, indazolyl, triazolyl, iso-quinolyl, quinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, naphthyridinyl, quinoxalyl, quinazolinyl, carbazolyl, β -carbolinyl, phen-anthridinyl, acridinyl, perimidinyl, phenanthrolinyl, furazanyl, phenazinyl, phenothiazinyl and phenoxazinyl, each of these radicals being unsubstituted or substituted by one to two radicals selected from the group consisting of fluoro, lower alkyl, especially methyl or tert-butyl, and lower alkoxy, especially methoxy.

An organic moiety R_1 or R_2 is preferably a moiety that comprises 1 to 50 carbon atoms, that may saturated, unsaturated or partially saturated, wherein carbon atoms may be replaced with heteroatoms, especially selected from N, O, S, Se or P, with the proviso that the moiety is chemically stable. The organic residue may in addition be substituted, or unsubstituted, preferably as described above.

Preferably, such an organic moiety is selected from the group consisting of an unsubstituted or substituted moiety selected from the group consisting of aryl, heterocyclyl, cycloalkyl, aryl-lower alkyl, heterocyclyl-lower alkyl, cycloalkyl-lower alkyl and alkyl.

Aryl preferably is as described above.

Heterocyclyl is preferably a heterocyclic radical that is unsaturated, saturated or partially saturated in the bonding ring and is preferably a monocyclic or in a broader aspect of the invention bicyclic or tricyclic ring; has 3 to 24, more preferably 4 to 16 ring atoms; wherein at least in the ring bonding to the radical of the molecule of formula I one or more, preferably one to four, especially one or two carbon ring atoms are replaced by a heteroatom selected from the group consisting of nitrogen, oxygen and sulfur, the bonding ring preferably having 4 to 12, especially 5 to 7 ring atoms; heteroaryl being unsubstituted or substituted by one or more, especially 1 to 3, substitutents independently selected from the group consisting of the substituents defined above under "Substituted"; especially being a heteroaryl radical selected from the group consisting of imidazolyl, thienyl, furyl, pyranyl, thiopyranyl, benzofuranyl, pyrrolinyl, pyrrolidinyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, thiazolyl, oxazolyl, pyridyl, pyrazinyl, pyrimidinyl, piperidyl, piperazinyl, pyridazinyl, morpho-

linyl, thiomorpholinyl, indolizinyl, isoindolyl, indolyl, benzimidazolyl, indazolyl, triazolyl, iso-quinolyl, quinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, benzofuranyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, naphthyridinyl, quinoxalyl, quinazolinyl, carbazolyl, β -carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, furazanyl, phenazinyl, phenothiazinyl and phenoxazinyl, each of these radicals being unsubstituted or substituted by one to two radicals selected from the group consisting of lower alkyl, especially methyl or tert-butyl, and lower alkoxy, especially methoxy.

Cycloalkyl is preferably C₃-C₁₀-cycloalkyl, especially cyclopropyl, dimethylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, cycloalkyl being unsubstituted or substituted by one or more, especially 1 to 3, substituents independently selected from the group consisting of the substituents defined above under "Substituted".

Aryl-lower alkyl is preferably lower alkyl that is substituted (preferably terminally or in 1-position) by unsubstituted or substituted aryl as defined above, especially phenyl-lower alkyl, such as benzyl.

Heterocycl-lower alkyl is preferably lower alkyl that is substituted (preferably terminally) by unsubstituted or substituted heterocycl as defined above.

Cycloalkyl-lower alkyl is preferably lower alkyl that is substituted (preferably terminally) by unsubstituted or substituted cycloalkyl as defined above.

Alkyl preferably has up to 20, more preferably up to 12 carbon atoms and is linear or branched one or more times; preferred is lower alkyl, especially C₁-C₄-alkyl.

Substituted alkyl is especially aryl-lower alkyl, heterocycl-lower alkyl or cycloalkyl-lower alkyl, wherein aryl- heterocycl or cycloalkyl are unsubstituted or substituted by one or more, preferably up to 4, subsituents independently selected from the substituents defined generally above.

An organic residue capable of binding to phosphorus preferably is any moiety that comprises 1 to 50 carbon atoms, that may saturated, unsaturated or partially saturated, wherein carbon atoms may be replaced with heteroatoms, especially selected from N, O, S, Se or P, with the

proviso that the moiety is chemically stable. The organic residue may in addition be substituted, or unsubstituted, preferably as described above. In the case of R_3 , "monovalent" means that the moiety is bound via one bond to the rest of the molecule (one hydrogen is replaced with this bond), in the case of R_3^* , bivalent means that the moiety is bound via two bonds to the rest of the molecule, preferably in a manner so that 5 to 7-membered cyclic phosphorus metal complexes are formed.

Preferably, an organic residue capable of binding to phosphorus is selected from the group consisting of an unsubstituted or substituted moiety selected from the group consisting of aryl, heterocyclyl, cycloalkyl, aryl-lower alkyl, heterocyclyl-lower alkyl, cycloalkyl-lower alkyl, alkyl, aryloxy, heterocyclyloxy, cycloalkyloxy, aryl-lower alkyloxy, heterocyclyl-lower alkyloxy, cycloalkyl-lower alkyloxy and alkoxy, with the more general moieties mentioned preferably being defined as above.

A lithiating reagent is preferably an organolithium compound, preferably an alkyl-lithium, especially a lower alkylolithium, preferably n-butyllithium or hexyllithium, or in a broader aspect sec- or tert-butyllithium, or aryl-lithium, such as phenyllithium. The reaction preferably takes place in the presence of a tertiary nitrogen base, preferably a complex forming one, especially N,N,N',N'-tetramethylendiamine (TMEDA) in a liquid alkane or mixture of liquid alkanes, such as hexane(s), an (anhydrous, especially absolute) ether, especially a di-lower alkylether, such as diethylether, or a cyclic ether, such as tetrahydrofuran, at preferred temperatures between -70 and 50 °C, especially between -50 and 45 °C, more preferably between -30 and 40 °C, preferably under inert gas, e.g. argon or nitrogen and under water-free conditions, e.g. using the Schlenk technology and equipment. For appropriate reaction conditions, see, e.g., Meyer, N., Seebach, D. *Chem. Ber.* 1980, 113, 1304.

An N,N-di-alkyl-formamide is preferably N,N-dimethylformamide (dimethylformamide). The reaction of a compound of the formula IIIA or IIIB with formamide preferably takes place in an appropriate solvent, e.g. as mentioned in the last paragraph, especially an alkane or alkanes mixture, such as hexane(s), at a preferred temperature from 0 to 50 °C, e.g. from 10 to 40 °C. The reaction with the N,N-dialkylformamide usually takes place in the reaction mixture resulting from the lithiation.

The temperature for the Grignard reaction is preferably elevated as then the selectivity towards the C_2 -symmetric diol is increased, preferably at a temperature between -30 °C and the reflux temperature of the reaction mixture, more preferably between 20 and 70 °C. The reaction preferably takes place in an aprotic solvent, especially an ether, such as a di-lower alkylether, or preferably a higher boiling ether, e.g. a cyclic ether, such as dioxane or especially tetrahydrofuran.

If a Grignard reagent R_2MgX is used wherein R_2 is an organic moiety different from R_1 in formula IIIA or IIIB, this furnishes a mixture of 1,4-diols IVA or IVB. If in the Grignard reagent R_2MgX R_2 is identical to R_1 , a mixture of symmetrical diols is formed. In this case the C_2 -symmetric diol is chiral AND enantiopure, whereas the C_s -symmetric diol is a meso compound. When the used Grignard reagent is of the type R_2MgX wherein R_1 is different from R_2 , again only two ENANTIOPURE diols are formed, one with local C_2 -symmetry, and the other with local C_s -symmetry.

Surprisingly, in typical cases it is found, that at low temperature (-30 °C) an almost 1:1 ratio of the enantiomeric to the meso is observed, whereas at elevated temperature (65 °C, refluxing THF) a mixture of the diols IVA or IVB (C_2 -symmetry) and VA (with IVA) or VB (with IVB) (C_s -symmetry) in a ratio 4:1 is obtained in 85% yield. The stereochemical assignment of IVA/IVB or VA/VB to be the chiral or meso-diol is based on the 1H -NMR of the acetonide. Here, IVA/IVB gives one signal and VA/VB two signals for the acetonide methyl groups, respectively, if $R_1 = R_2$.

Halogen is preferably fluoro, chloro, bromo or iodo, more preferably chloro, bromo or iodo.

In the second preferred variant, the reaction with an aldehyde of the formula VI with a compound of the formula II A or II B preferably takes place directly in the lithiation mixture.

In this second variant, the resulting ration of IVA : VA or IVB : VB may typically be around 45 : 55, but the reaction allows for one pot synthesis and the use of starting materials that are conveniently accessible and thus provide a very pragmatic synthesis of the desired products which is highly advantageous.

The obtained products can be purified and, where required to isolate the pure isomers, separated according to standard methods, for example by chromatographic or solution crystallization methods.

In the first alternative for the manufacture of ligands of the formulae XA or XB^* , the reaction of a compound of the formula IVA or IVB (or either a mixture of a compound of the formula IVA and of the formula VA given below, or a mixture of a compound of the formula IVB and of the formula VB given below; or a compound of the formula VA given below or of the formula VB given above), respectively, with a diaryl phosphonic acid halogenide of the formula VII , takes place in the presence of a base preferably takes place at preferred temperatures in the range from -10°C to 80°C , preferably with a tertiary amine as base in an appropriate solvent, e.g. an ether, such as diethylether, a cyclic ether, such as tetrahydrofuran, an aromatic hydrocarbon, such as toluene or xylene. The resulting product of the formula $VIIIA$ or $VIIIB$, respectively, is then, in order to obtain a compound of the formula XA , XA^* , XB or XB^* , respectively, reacted with the corresponding compound of the formula IX (or the corresponding borane adduct of the formula $R_3\text{-PH}_2\bullet\text{BH}_3$) or IX^* (or the corresponding borane adduct of the formula $\text{BH}_3\bullet\text{H}_2\text{P-}R_3^*\text{-PH}_2\bullet\text{BH}_3$) preferably with a tert-alkyllithium, such as tert-butyllithium, in an inert solvent, such as an aromatic solvent, e.g. toluene, anisol or xylene, or a di-lower alkanesulfoxide, such as dimethylsulfoxide. For other leaving groups, such as those mentioned above, alkoholates of alkali metal hydroxydes, such as potassium tert-butylate or potassium hydroxide, N,N -di-(lower alkyl)-lower alkanoylamides, such as dimethylformamide, or dimethylsulfoxide are also acceptable.

In the alternative route via the compounds of the formulae IVA^* or IVB^* , or IVA^* and VA^* or IVB^* and VB^* , the diol starting materials are reacted with the acyl halogenides preferably in the presence of a tertiary nitrogen base, such as triethylamine or pyridine to yield the corresponding hydroxy-acylated derivatives. Subsequently, the reaction with a compound of the formula IX or IX^* takes place preferably in an inert solvent, such as a cyclic or acyclic ether, e.g. tetrahydrofuran or diethylether in the presence of a strong base, such as lithium diisopropylamide or a lower-alkyllithium, such as tert-butyllithium, or in a N,N -di-lower alkyl-lower alkanoylamine (especially N,N -dimethylformamide) and/or a di-lower alkanesulfoxide (especially dimethylsulfoxide) in the presence of a metal hydroxide, especially an alkali metal hydroxide, such as sodium or potassium hydroxide, or an alkali metal alcoholate, such as a sodium or potassium lower alkoxide.

In the alternative use of the compounds of the formula IVA or IVB for the production of ligands of the formula XIIA or XIIIB, or XIIA* or XIIIB*, the reaction with a compound of the formula XI or XI* preferably takes place under the following reaction conditions: The reaction with a compound of the formula XI or XI* preferably takes place in the presence of a base, especially a tertiary nitrogen base, such as pyridine or triethylamine. As solvent, inert solvents, especially ethers, such as tetrahydrofuran or diethylether, are preferred. The preferred reaction temperature lies in the range from -10 to 40 °C. The reaction takes place under exclusion of water and oxygen.

A leaving group L is preferably the moiety of an organic or inorganic acid remaining after removal of the acidic hydrogen, more preferably halogen, especially chloro or bromo.

The reaction with a compound of the formula XI** or XI***, on the other hand, preferably takes place in an inert solvent such as an aromatic hydrocarbon, e.g. toluene or xylene, preferably at temperatures from 50 °C to reflux, e.g. at the reflux temperature of the reaction mixture.

In the third alternative use/method using the compounds of formula IVA or IVB in the manufacture of ligands, the reaction of a compound of the formula IVA or IVB with a compound of the formula XIII preferably takes place under the same conditions as described for the reaction of compounds of the formula IVA or IVB with a compound of the formula XI or XI*, the reaction with a compound of the formula XIII* preferably as described for the reaction of compounds of the formula IVA or IVB with a compound of the formula XI** or XI***.

A leaving group L is preferably as defined above.

Complexes with transition metals of compounds of the formula XA, XB, XIIA, XIIIB, XIVA and/or XIVB are preferably those of these ligands together with transition metals, especially of groups 3 to 12 of the periodic table of elements, including the lanthanides and actinides, especially of groups 4 to 12, most especially with rhodium, ruthenium, palladium, platin, iridium, nickel or cobalt, preferably with rhodium or ruthenium.

Free ligand positions may in addition be occupied by further ligands, and/or counterions may be present.

The formation of transition metal complexes of compounds of the formula XA, XB, XIIA, XIIB, XIVA and/or XIVB can follow methods that are known in the art. In particular, in the complex used as starting material the transition metal is utilized in coordination with ligands such as 1,5-cis-cyclooctadiene, norbornadiene, (ethylene)₂, triarylstilbene, benzonitrile and the like. Counterions may also be present, depending on the charge of the resulting complex, e.g. BF_4^- , PF_6^- , SbF_5^- or CF_3SO_3^- , or lower alkanoates, such as acetate⁻.

For the manufacture of the complex, for example the complex constituted from the selected transition metal and the original ligand to be replaced is dissolved in a suitable solvent, e.g. an ether, such as a cyclic ether, preferably tetrahydrofuran, a halogenated hydrocarbon, such as a chlorinated lower alkane, e.g. chloroform or dichloromethane, an alcohol, such as methanol or ethanol, an aromatic hydrocarbon, such as toluene or xylene, or an N,N-di-(lower alkyl)-lower alkanoylamide, such as dimethylformamide; if required, in the presence of a further anionic ligand able to coordinate to remaining free coordination positions, and the chiral ligand is added, either in the solid state or already dissolved in a suitable solvent. The progress of the reaction may, inter alia, be followed by detection of colour changes, precipitation of the product, NMR, GC, TLC or the like. At the end of the reaction, the solvent is removed and the chiral complex formed may be used as it is or it may be subjected to further standard purification steps known in the art in order to obtain a purified complex. Preferably, the complex formation takes place shortly or immediately before the use of the complex in organic synthesis, e.g. hydrogenation.

All reactions described hereinbefore and hereinafter are preferably, where required, mandatorily, carried out under inert gas, e.g. argon or nitrogen and (where required or desirable) under water-free conditions, e.g. using the Schlenk technology and equipment and anhydrous (especially absolute) reagents and solvents.

The invention relates also to any novel single reaction step that forms part of the synthesis of compounds of the formula IVA and/or IVB, as well as of those of formula XA and/or XB, as well as of those of the formula XIIA and/or XIIB, as well as those of the formula XIVA and/or

XIVB, or complexes of the ligands of the formulae XA, XB, XIIA, XIIIB, XIVA and/or XIV, as well as to any novel intermediate formed during these synthesis steps.

Preferred embodiments of the invention can be found in the claims which are incorporated herewith by reference into the description.

Very preferred embodiments of the invention, especially of the C_2 symmetric diols, and of the ligands, as well as methods synthesis of the diols or ligands, respectively, according to the invention are mentioned in the following examples and claims. Also preferred are metal complexes comprising the ligand groups or ligands mentioned in the examples.

EXAMPLES

The following examples illustrate the invention without limiting the scope thereof.

Abbreviations:

n-BuLi	n-butyllithium
NMR	Nuclear Magnetic Resonance
THF	tetrahydrofuran
TMEDA	N,N,N',N'-tetramethylethylene diamine

Example 1:

A: Mixture of cis/trans (3R)- 3-methyl-1,3-dihydro-isobenzofuran-1-ol: A solution of (1*R*)-1-phenylethanol (2.0 g, 16.37 mmol) and TMEDA (4.0 g, 34.35 mmol) in hexanes (20 mL) is cooled to -10°C, and then a solution of n-BuLi in hexanes (2.5 N, 13.8 mL, 34.38 mmol) is added within 15 minutes. The temperature is maintained in the range between -10 and -5 °C during the addition. The mixture is then allowed to warm to ambient temperature, and finally kept at 40°C over night. DMF (2.4 g, 32.74 mmol) is then added within 10 minutes to the formed beige suspension, maintaining a temperature lower than 30°C. When the addition is complete, the mixture is stirred for another hour, and then hydrolyzed carefully with water. The organic layer is washed with water and brine, and dried (Na_2SO_4). Removal of the solvent leaves an orange oil (2.6 g), which is chromatographed on silica with ethyl

acetate/hexane 1:2 to give the title product as pale yellow oil (1.51 g, 61%) as a ca. 1:1 mixture of both diastereoisomers. $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 1.47 (d, J = 6.2 Hz), 1.56 (d, J = 6.5 Hz) (CH_3); 3.97 (br s, OH); 5.22 (q, J = 6.5 Hz), 5.48 (dq, J = 6.2 Hz, J = 0.9 Hz) (CH); 6.39 (br s), 6.46 (br s) (CH); 7.15-7.42 (m) (Ph-H). $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 21.86, 24.04 (CH_3); 78.87, 79.60 (CH); 100.62, 101.04 (CH); 121.09, 121.20 (CH); 123.11, 123.19 (CH); 128.10, 128.12 (CH); 129.48, 129.49 (CH); 139.14, 139.21 (C); 144.01, 144.05 (C).

B: Mixture of (*R,R*)- and (*R,S*)-[2-(1-Hydroxy-ethyl)-phenyl]-ethanol:

A solution of (*3R*)- 3-methyl-1,3-dihydro-isobenzofuran-1-ol (500 mg, 3.32 mmol) in THF (5 mL) is heated to 60°C, and to this a solution of methyl magnesium bromide (2.77 mL 3 N solution in ether; 8.32 mmol) is added within 10 minutes. The mixture is heated at 60°C for another 30 minutes. After cooling the mixture is poured in water. The product is extracted with ethyl acetate, and removal of the solvent gives an oil which is a 63:37 mixture of the chiral and meso-diol title product. When the same reaction is performed at a temperature of -30°C, the ratio of chiral:meso diol is 52:48. $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): δ 1.50 (d, J = 6.2 Hz, meso CH_3); 1.52 (d, J = 6.4 Hz, chiral CH_3); 3.12 (br s, OH); 5.15 (q, meso CH); 5.19 (q, chiral CH); 7.25-7.32, 7.39-7.48 (2 m, Ph-H). $^{13}\text{C-NMR}$ (CDCl_3 , 75 MHz) δ 23.58 (meso CH_3); 24.80 (chiral CH_3); 65.50 (meso CH); 67.43 (chiral CH); 125.48 (meso Ph-CH); 126.19 (chiral Ph-CH); 128.00 (chiral Ph-CH); 128.09 (meso Ph-CH); 142.10 (meso Ph-C); 142.30 (chiral Ph-C).

Example 2:

A: Mixture of cis/trans (*3R*)- 3-ethyl-1,3-dihydro-isobenzofuran-1-ol:

A solution of (*1R*)-1-phenylethanol (5.0 g, 36.7 mmol) and TMEDA (8.96 g, 77.1 mmol) in hexanes (50 mL) is cooled to -10°C, and then a solution of n-BuLi in hexane (10 N, 7.71 mL, 77.1 mmol + 10 mL of hexane) is added within 15 minutes. The temperature is maintained in the range between -10 and -5 °C during the addition. The mixture is then allowed to warm to ambient temperature, and finally heated at 40°C over night. DMF (5.37 g, 73.42 mmol) is then added within 10 minutes to the formed beige suspension, maintaining a temperature lower than 30°C. When the addition is complete, the mixture is stirred for another hour, and then hydrolyzed carefully with water. The organic layer is washed with water and brine, and dried (Na_2SO_4). Removal of the solvent leaves an orange oil (7.4 g), which is chromatographed on silica with ethyl acetate/hexane 1:2 to give the title product as pale yellow oil (3.03 g, 50%) as a ca. 1:1 mixture of both diastereoisomers. $^1\text{H-NMR}$ (CDCl_3 , 300

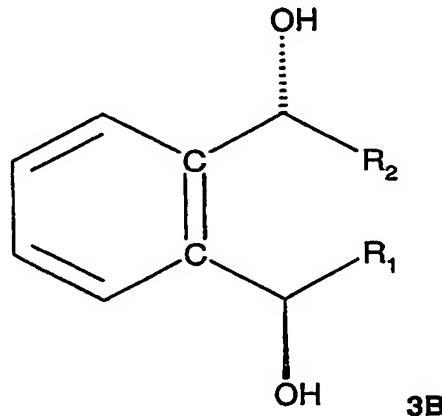
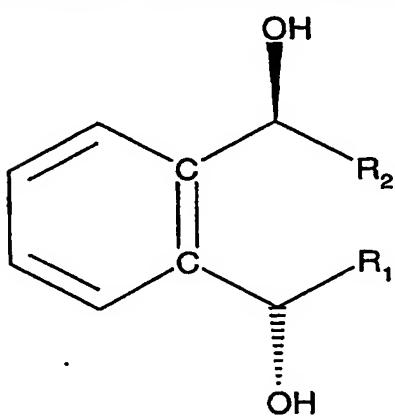
MHz) δ 0.93 (tr, J = 7.3 Hz, A CH₃); 1.01 (tr, J = 7.3 Hz, B CH₃); 1.62-2.03 (m, A+B CH₂); 3.87 (br s, B OH); 3.98 (br s, A OH); 5.11 (dd, J = 4.4 Hz, J = 6.5 Hz, B CH); 5.37 (ddd, J = 2.1 Hz, J = 4.2 Hz, J = 6.6 Hz, A CH); 6.41 (s, B CH); 6.47 (d, J = 2.1 Hz, A CH); 7.15-7.21, 7.27-7.43 (m, Ph H). ¹³C-NMR (CDCl₃, 75 MHz) δ 9.36 (A CH₃); 9.85 (B CH₃); 28.98 (A CH₂); 30.47 (B CH₂); 83.79 (A CH); 84.67 (B CH); 100.89 (B CH); 100.92 (A CH); 121.29 (A CH); 121.41 (B CH); 123.13 (A CH); 123.20 (B CH); 128.12 (A+B CH); 129.37 (B CH); 129.41 (A CH); 139.53 (B C); 139.72 (A C); 142.46 (A C); 142.54 (B C).

B: Mixture of (R,R)- and (R,S)-1-[2-(1-Hydroxy-propyl)-phenyl]-propan-1-ol:

A solution of (3*R*)- 3-ethyl-1,3-dihydro-isobenzofuran-1-ol (500 mg, 3.04 mmol) in THF (5 mL) is heated to 60°C, and a solution of ethyl magnesium bromide (2.54 mL, 3 N solution in ether; 7.61 mmol) is added to this mixture within 5 minutes. The mixture is heated at 60°C for another 30 minutes. After cooling the mixture is poured in water, and the pH is adjusted to 6 by adding 1 N HCl. The product is extracted with ethyl acetate, and removal of the solvent gives an oil (0.61 g, quant.) which is a 80:20 mixture of the chiral and meso-diol. ¹H-NMR (CDCl₃, 300 MHz) δ 0.85 (tr, J = 7.3 Hz, CH₃); 1.60-1.80 (m, CH₂); 2.81 (br s, OH); 4.72 ("tr", J = 6.5 Hz, meso CH); 4.76 ("tr", J = 6.2 Hz, chiral diol); 7.13-7.19 (m, Ph-CH); 7.24-7.34 (Ph CH). ¹³C-NMR (CDCl₃, 75 MHz) δ 9.66 (CH₃); 29.31 (meso CH₂); 30.20 (chiral CH₂); 69.40 (meso CH); 71.56 (chiral CH); 124.60 (meso Ph CH); 125.31 (chiral Ph CH); 126.36 (chiral Ph CH); 126.45 (meso Ph CH); 140.10 (Ph C).

Example 3: Further Examples

In analogy to example 2, the following compounds of formula IVA or IVB are prepared:



Compound

R₁

R₂

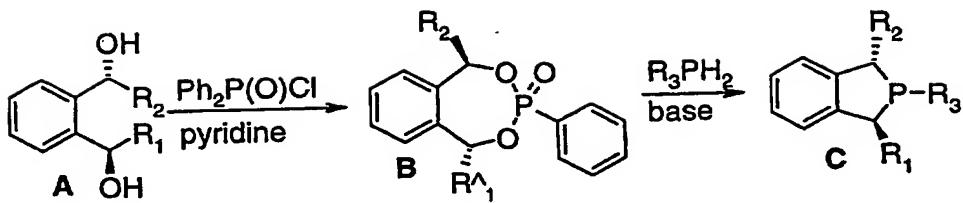
1/3A	methyl	methyl
2/3A	ethyl	ethyl
3/3A	n-propyl	n-propyl
4/3A	isopropyl	isopropyl
1/3B	methyl	methyl
2/3B	ethyl	ethyl
3/3B	n-propyl	n-propyl
4/3B	isopropyl	isopropyl

Example 5: (4R,7R)-4,7-Dimethyl-3-phenyl-1,5-dihydro-benzof[e][1,3,2]dioxaphosphhepine 3-oxide

Starting with the title compound from Example 1 B, the title compound is prepared. In an analogous example, to a solution of meso-[1(2-{1-hydroxyethyl}phenyl)—1-ethynol (17.4 g, 0.1 mol) in pyridine (24.8 g, 0.3 mol), a solution of phenylphosphonic acid dichloride (20.4 g, 0.1 mol) in dichloromethane (10 ml) is added at a temperature of 0 °C. The resulting mixture is then stirred for 1 h and then diluted with dichloromethane (100 ml). The mixture is subsequently poured into 2N HCl (200 ml) and mixed thoroughly. The organic layer is separated and washed twice with water. After removal of the solvent, the product is obtained as colorless solid. Yield: 30.1 g (quantitative). ¹H-NMR (CD₂Cl₂, 500 MHz): δ 1.87 (d, 6H, J = 6.4 Hz, CH₃); 6.25 (q, 2H, CH); 7.28-7.78 (m, 9H, Ph-H). ¹³C-NMR (CD₂Cl₂, 125 MHz); δ 19.87 (CH₃); 69.97 (CH); 128.35, 128.35, 128.78, 125.81, 128.88, 131.63, 132.97 (Ar-C) **bitte checken!**; ³¹P-NMR (CD₂Cl₂, 202 MHz): δ = 20.35.

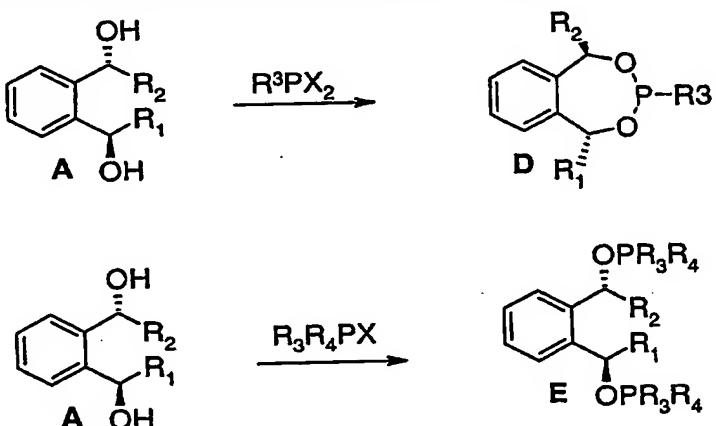
Example 6:

Reaction of **A** with phenylphosphonic acid chloride gives the cyclic phosphonate ester **B** in quantitative yield. When **B** is reacted with a primary phosphine in the presence of tert-butyllithium under reflux in toluene, the hitherto unknown benzophospholanes **C** are formed. There are no limitations to R₃, as long as this can bind stable to phosphorus. It is worthy to note, that there is little precedence for nucleophilic substitution with inversion of benzylic positions. A cyclic sulfate of **A** (with R = Me), which should react similarly like **B**, decomposes very rapidly after it has been prepared.



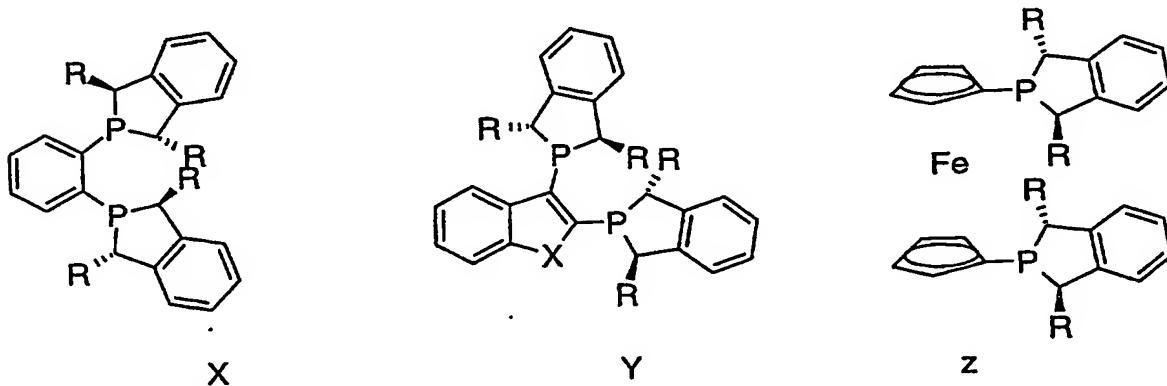
R₁ and R₂ have the meanings indicated above for compounds of the formula IVA or IVB, R₃ is an organic moiety that can be bound to phosphorus.

Example 7: Another use of diols such as A in Example 4 is their conversion into ligands of type D or E. The synthesis of these compounds follows standard procedures where a phosphorus compound with a suitable leaving group X is reacted with the diol.

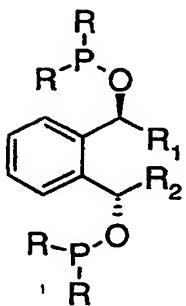
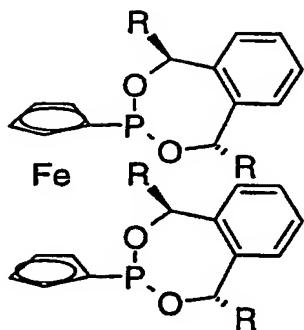
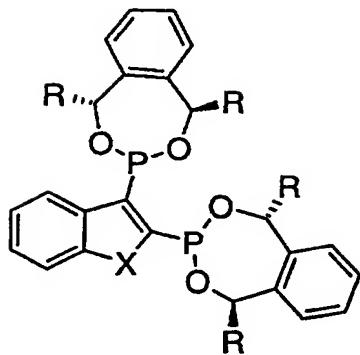


Herein, R₃ or R₄ may be any group that can be bound to phosphorus.

Example 8: The following ligands are prepared in analogy to the methods described in examples 6 and 7:



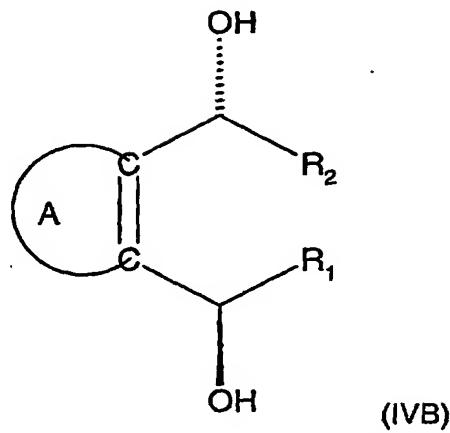
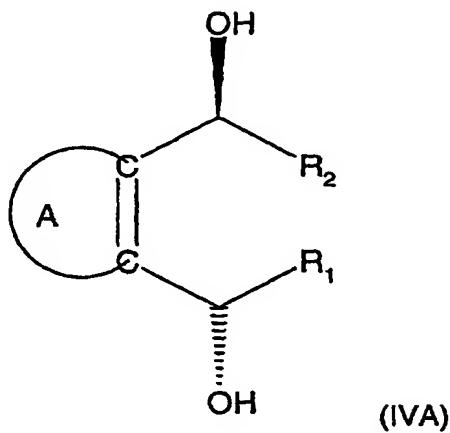
R = identical and selected from methyl, ethyl, isopropyl, n-propyl and tert-butyl ; X = O, S or N.



X = N, O or S. R = methyl, ethyl, isopropyl, tert-butyl; R₁ = R₂ = selected from alkyl, especially lower alkyl, aryl, especially phenyl, or heterocyclyl, especially 2-thienyl.

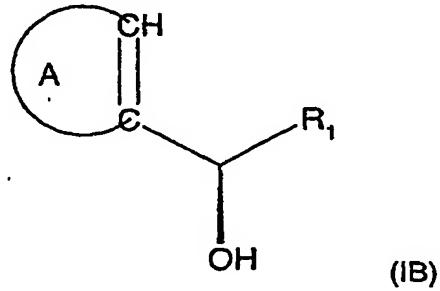
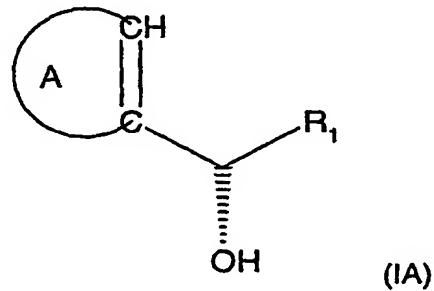
What is claimed is:

1. A method for the preparation of an enantiomerically pure C_2 -symmetric 1,4-diols of the formula IVA or IVB,

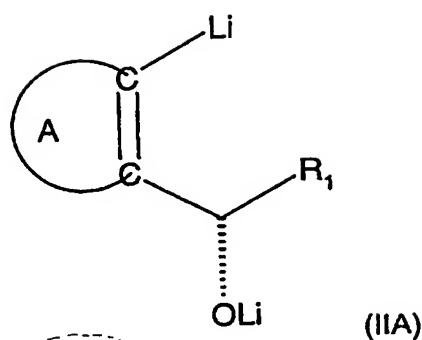


wherein ring A which includes the shown double bond forms a mono-, di- or polycyclic aromatic or heteroaromatic ring and R₁ and R₂ are, independently of each other, an organic moiety,

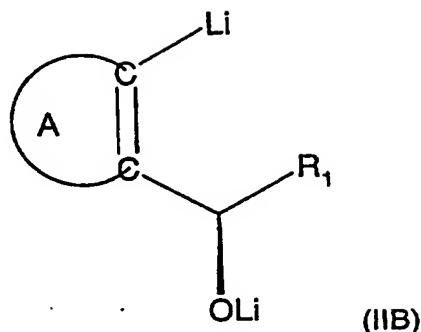
the process or method comprising reacting an α -(aryl or heteroaryl)- α -substituted alkanol compound of the formula IA (for the synthesis of a compound of the formula IVA) or IB (for the synthesis of a compound of the formula IVB)



wherein ring A and R₁ are as defined under formula IVA and IVB, with a lithiating reagent, obtaining an intermediate of the formula IIA (from IA) or IIB (from IB),



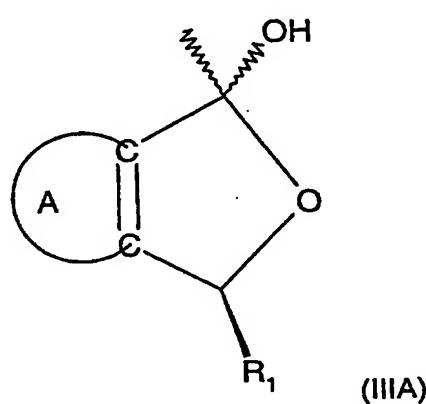
(IIA)



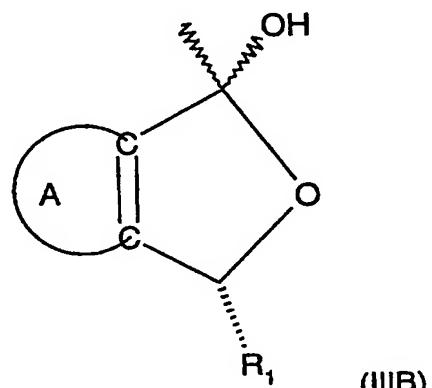
(IIB)

wherein ring A and R₁ have the meanings given under compounds of the formulae IVA and IVB.

2. The process according to claim 1, further comprising reacting the lithiated product of the formula IIA or IIB, respectively, with an N,N-di-alkyl-formamide to a hemiacetal compound of the formula IIIA (from IIA) or IIIB (from IIB).



(IIIA)



(IIIB)

wherein ring A, R₁ and R₂ have the meanings indicated for compounds of the formula IVA and IVB, and subsequently with a Grignard reagent of the formula R₂MgX wherein R₂ is an organic moiety and X is halogen or, alternatively, using corresponding lithium, zinc or other metal comprising compounds that allow for introduction of R₂; to yield the corresponding compounds of formula IVA (from IIIA) and IVB (from IIIB).

3. The method according to claim 1, further comprising reacting an aldehyde of the formula VI



wherein R_2 is as defined for compounds of the formulae IVA and IVB, with the intermediate of the formula IIA to yield a compound of the formula IVA or of the formula IIB to yield a compound of the formula IVB.

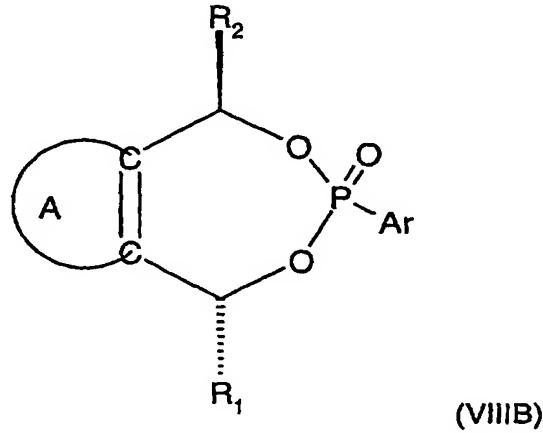
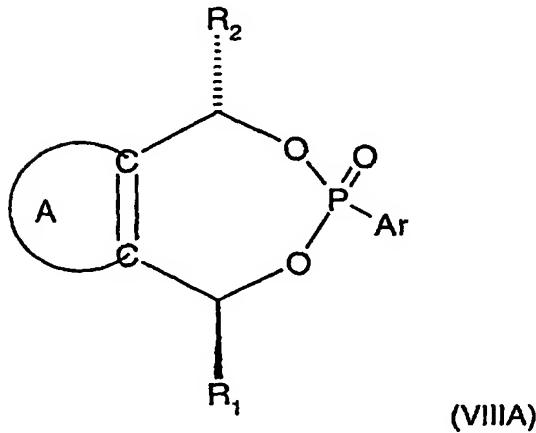
4. A compound of the formula IVA or IVB as shown in claim 1, wherein ring A, R_1 and R_2 are as defined in claim 1, with the proviso that R_1 and R_2 are not simultaneously methyl or ethyl.

5. A process for the preparation of a ligand of the formula XA , XA^* , XB or XB^* given below,

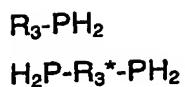
said process comprising reacting a compound of the formula IVA (for the synthesis of a compound of the formula XA) or IVB (for the synthesis of a compound of the formula XB) obtained according to any one of claims 1 to 3 with an aryl phosphinic acid halogenide of the formula VII;



wherein Ar is aryl, especially phenyl, and Hal is halogen, especially chloro, in the presence of a base resulting in the formation of a phosphonate ester compound of the formula VIIIA (from IVA) or VIIIB (from IVB), respectively,



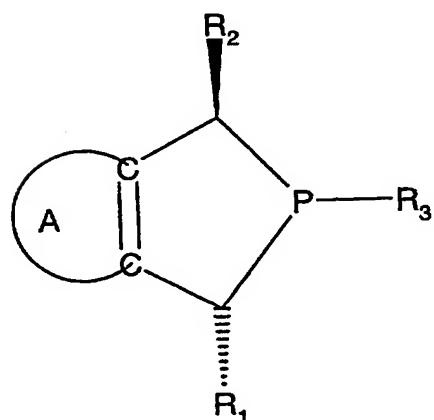
wherein ring A, R_1 and R_2 have the meanings indicated for compounds of the formula IVA and IVB and Ar is aryl, and then reacting a compound of the formula VIIIA or VIIIB with a phosphine of the formula IX or IX*,



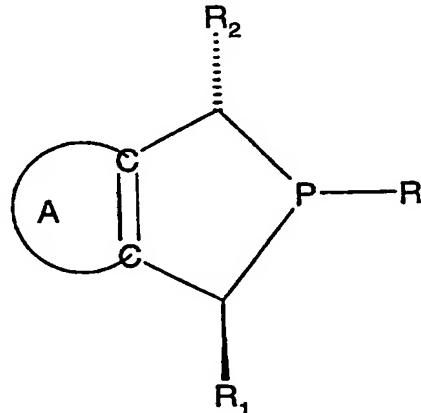
(IX)

(IX*)

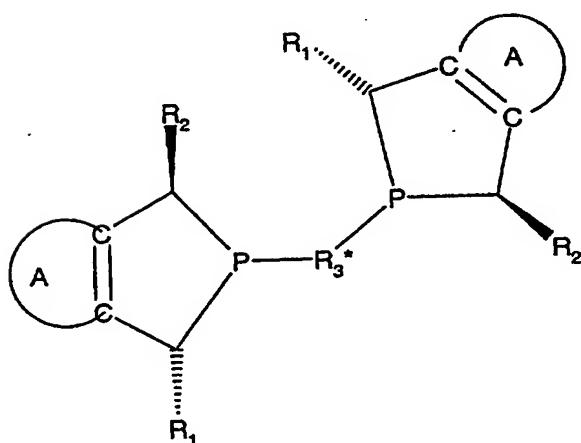
(or the corresponding borane adduct thereof) wherein R_3 is a monovalent, R_3^* a bivalent organic moiety that can be bound to phosphorus, resulting in a phospholane compound of the formula XA or XA^* (from VIIIA); or XB or XB^* (from VIIIB), respectively,



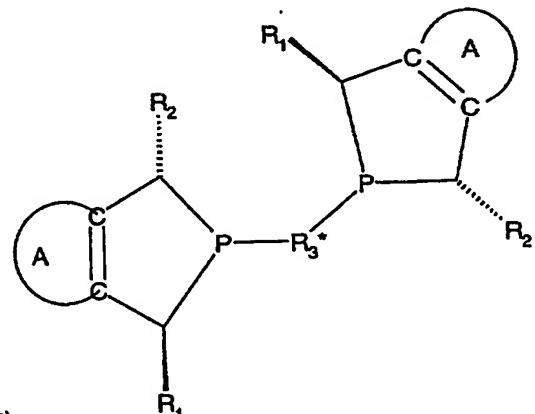
(XA)



(XB)



(XA*)



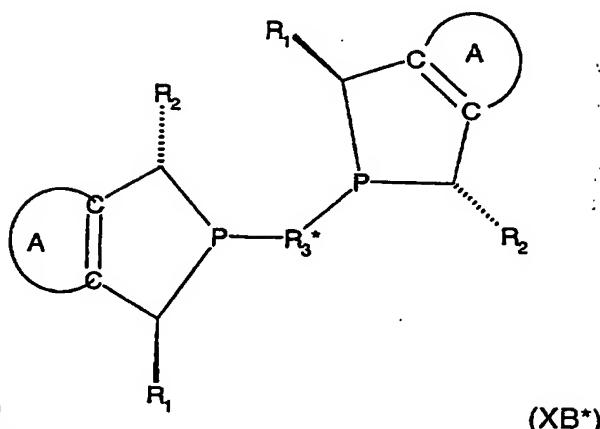
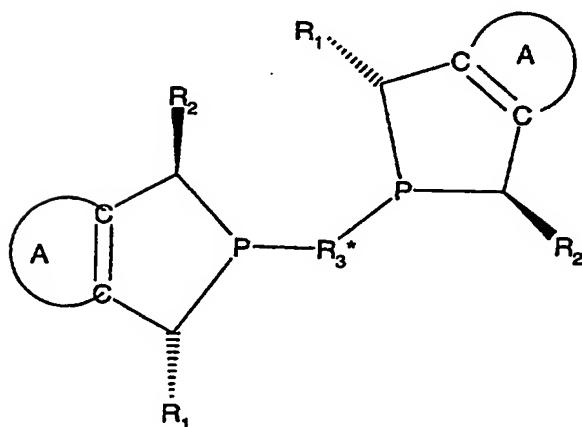
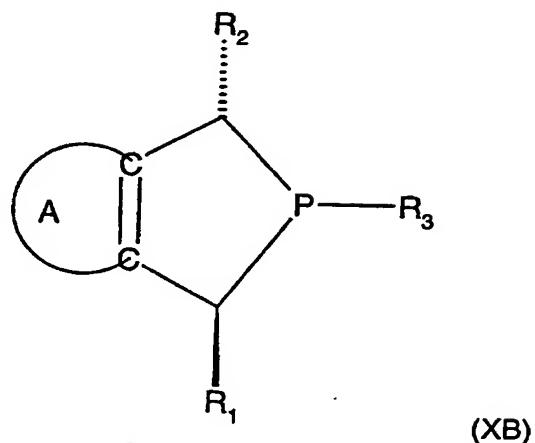
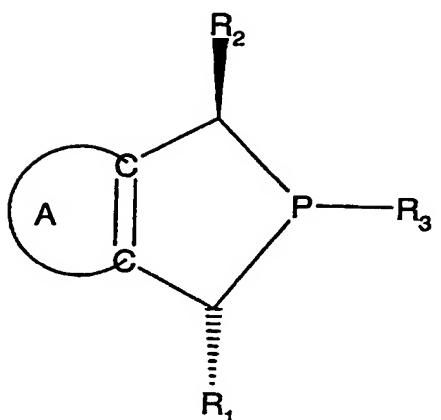
(XB*)

wherein ring A , R_1 and R_2 have the meanings indicated for compounds of the formula IVA or IVB and R_3 or R_3^* is as defined under formulae IX and IX*, respectively.

6. A ligand of the formula XA , XA^* , XB or XB^* , as shown and defined in claim 5.

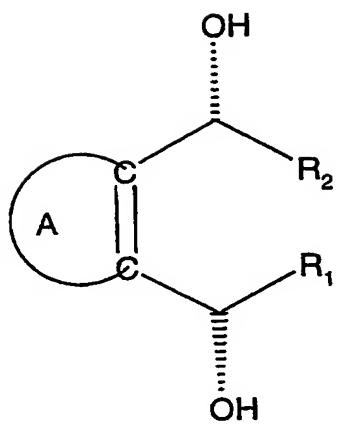
7. A transition metal complex comprising a ligand of the formula XA , XA^* , XB or XB^* , as shown and defined in claim 5.

8. A process for the preparation of a compound of the formula XA , XA^* , XB or XB^* ,

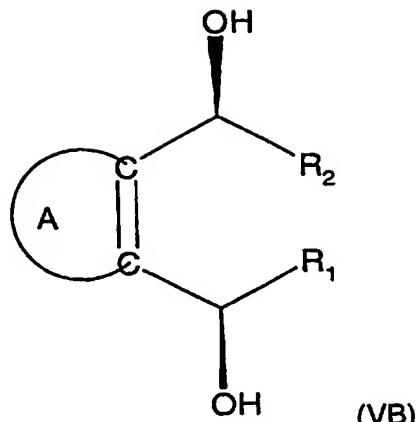


wherein ring A, R_1 and R_2 have the meanings indicated for compounds of the formula IVA or IVB in claim 1 and R_3 or R_3^* is as defined under formulae IX and IX*, respectively

said process comprising reacting a compound of the formula IVA or IVB given in claim 1, or a mixture of a compound of the formula IVA and VA, or of a compound of the formula IVB and VB,



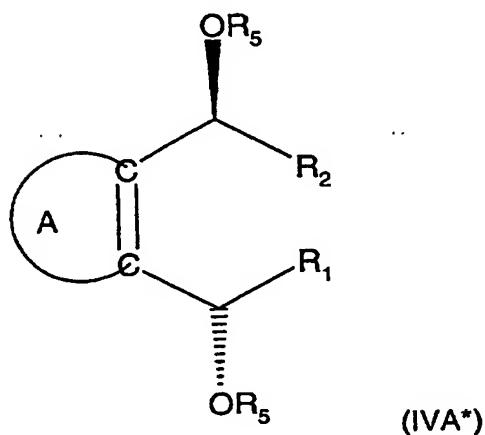
(VA)



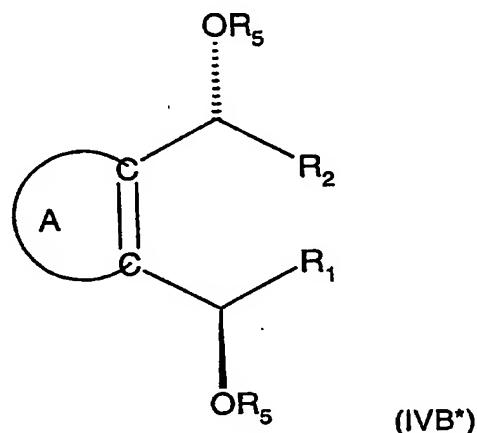
(VB)

wherein ring A, R₁ and R₂ have the meanings indicated for compounds of the formula IVA and IVB,

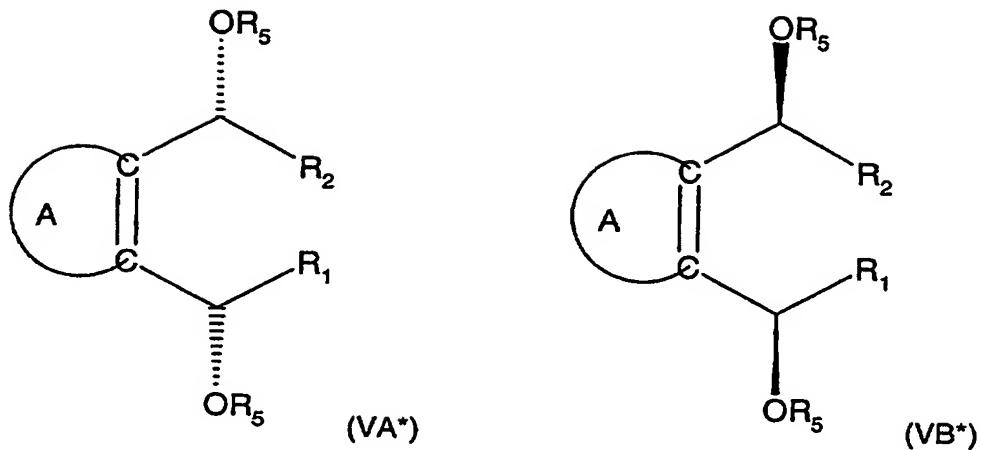
with an agent introducing an acyl protecting group, obtaining the corresponding bis-hydroxy-protected compounds of the formula IVA* (from IVA), IVB* (from IVB), or mixtures of a compound of the formula IVA* and VA* (from a mixture of a compound of the formula IVA and VA) or of a compound of the formula IVB* and VB* (from a mixture of a compound of the formula IVB and VB),



(IVA*)



(IVB*)



wherein ring A, R₁ and R₂ have the meanings indicated for compounds of the formula IVA and IVB and R₅ is acyl, and then reacting the compound or compounds to the corresponding compounds of the formulae XA shown above with a compound of the formula IX,



or a borane adduct thereof, wherein R₃ is a monovalent organic moiety that can be bound to phosphorus,

or for a compound of the formula XA* shown above with a compound of the formula IX*,



or a borane adduct thereof, wherein R₃* is a bivalent organic moiety that can be bound to phosphorus, in both cases starting from a compound of the formula IVA*(alone or less preferably in mixture with a compound of the formula VA*);

or of the formula XB shown above with a compound of the formula IX shown above or a borane adduct thereof, or to a compound of the formula XB* shown above with a compound of the formula IX* shown above or a borane adduct thereof, in both cases starting from a compound of the formula from IVB* (alone or less preferably in mixture with a compound of the formula VB*),

in the case of mixtures of compounds of the formula IVA* and VA* or IVB* and VB* preferably after isolating the compounds of the formula IVA* or IVB*, respectively, from the undesired enantiomer of the formula VA* or VB*.

9. The process according to claim 8, further comprising reacting the compound of the formula VIIIA or VIIIB with a phosphine of the formula IX or IX*,

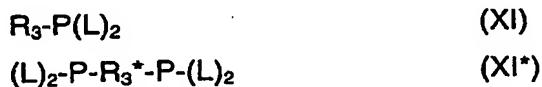


(or the corresponding borane adduct thereof) wherein R_3 is a monovalent, R_3^* a bivalent organic moiety that can be bound to phosphorus, resulting in a phospholane compound of the formula XA or XA* (from VIIIA); or XB or XB* (from VIIIB) shown in claim 5, respectively.

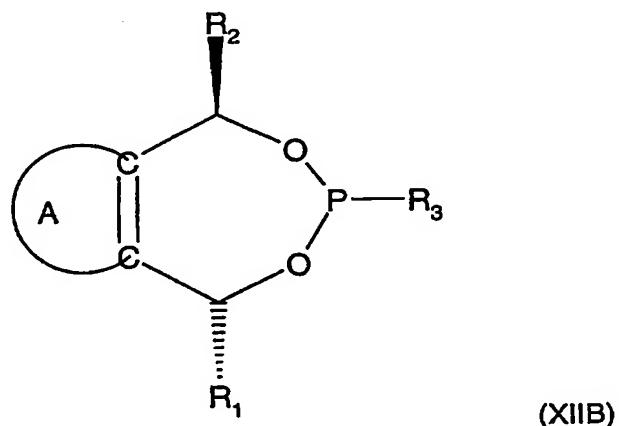
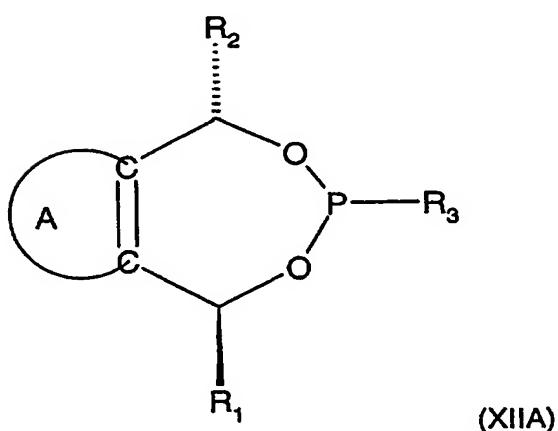
10. A process for the preparation of a ligand of the formula XIIA or XIIA* shown below from a compound of the formula IVA or of the formula XIIIB or XIIIB* shown below from a compound of the formula IVB,

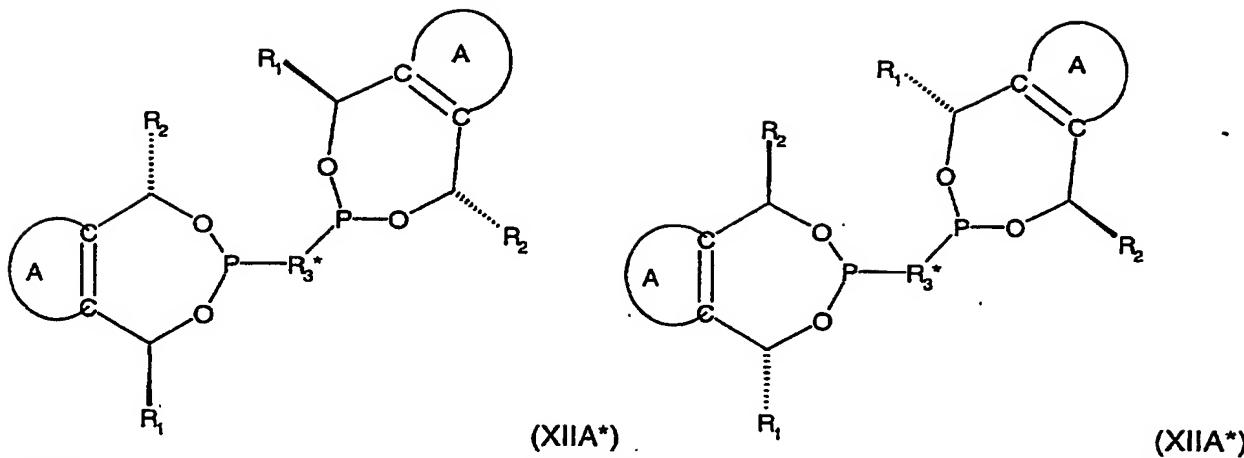
comprising

a) reacting a compound of the formula IVA or IVB with a compound of the formula XI or XI*,



wherein R_3 is a monovalent, R_3^* a bivalent organic moiety that can be bound to phosphorus and L is a leaving group, leading to ligands of the formula XIIA or XIIA* (from IVA) and/or XIIIB or XIIIB* (from IVB),





wherein ring A, R₁ and R₂ have the meanings indicated for compounds of the formula IVA and IVB and R₃ is a monovalent, R₃* a bivalent organic moiety that can be bound to phosphorus; or

b) reacting a compound of the formula IVA or IVB with a compound of the formula XI** or XI***,

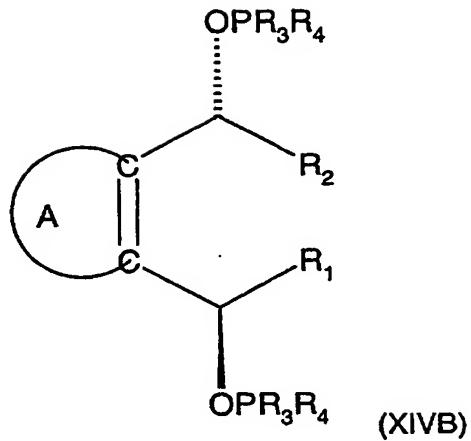
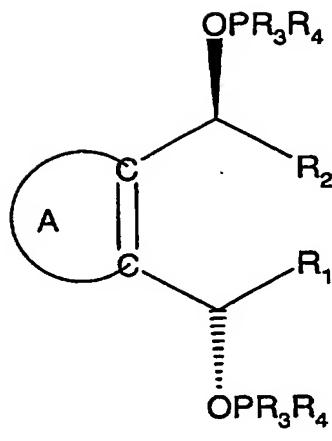


wherein R₃ is a monovalent, R₃* a bivalent organic moiety and alk is alkyl, especially lower alkyl, in particular methyl, under removal of the secondary amine HN(alk₂)₂, yielding the compound of formula XIIA or XIIA* (from IVA); or XIIB or XIIB* (from IVB) described above, respectively.

11. A ligand of the formula XIIA, XIIA*, XIIB or XIIB*, as shown in claim 10.

12. A transition metal complex comprising a ligand of the formula XIIA, XIIA*, XIIB or XIIB*, as shown in claim 10.

13. A process for the preparation of a ligand of the formula XIVA from a compound of the formula IVA or of the formula XIVB from a compound of the formula IVB,



wherein ring A, R₁ and R₂ are as defined for compounds of the formula XIVA or XIVB in claim 1 and R₃ and R₄ each are, independently of the other, an organic moiety that can be bound to phosphorus,

said process comprising reacting a compound of the formula IVA or VIB given in claim 1, respectively, with

a) a compound of the formula XIII,



wherein R₃ and R₄ are organic moieties that can be bound to phosphorus and L is a leaving group, resulting in a compound of the formula XIVA (from IVA) or XIVB (from IVB), respectively; or

b) with a compound of the formula XIII*,



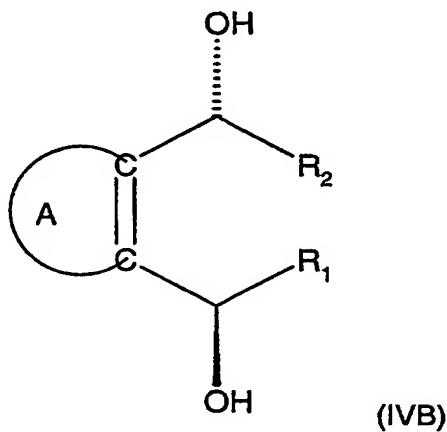
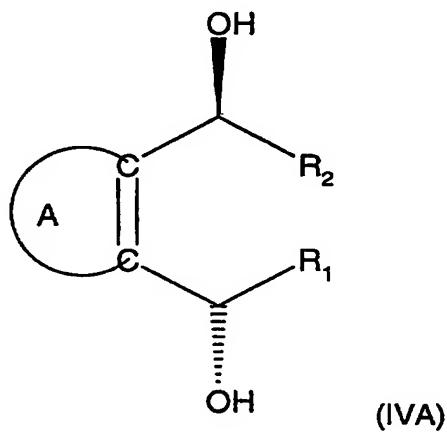
wherein R₃ is an organic moiety and alk is alkyl, especially lower alkyl, in particular methyl, under removal of the amine H₂N(alk)₂

14. A ligand of the formula XIVA or XIVB, as shown in claim 13.
15. A transition metal complex comprising a ligand of the formula XIVA or XIVB, as shown in claim 13.
16. The use of a phosphorus containing ligand according to any one of claims 6, 11 and 14 or a transition metal complex of either ligand type according to any one of claims 7, 12 and 15 in an asymmetric reaction or as an asymmetric catalyst.

Abstract

New chiral diols, their manufacture and ligands and catalysts derived therefrom

The present invention relates to a method for the preparation of C_2 -symmetric 1,4-diols of the formula IVA or IVB,



wherein ring A, R₁ and R₂ have the meanings given in the specification, that makes use of the metallation of pure enantiomers of α -(aryl or heteroaryl)- α -substituted alkanol compounds or the use of said alkanol compounds in the preparation of said symmetric 1,4-diols; novel C_2 -symmetric 1,4-diols in enantiomerically pure form; and methods of use or their use in the synthesis of chiral ligands which find use to produce catalysts for a variety of asymmetric transformations such as hydrogenations.

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